Experience with Nalidixic Acid in the Treatment of Urinary Tract Infections of Children

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Nalidixic acid is one of the latest chemotherapeutic agents to be used in the treatment of urinary tract infections. It is one of a series of naphthyridine derivatives investigated by Leshner, Froelich, Gruett, Bailey, and Brundage (1962), and is 1-ethyl-7-methyl-1, 8-naphthyridine-4-one-3-carboxylic acid, with the structural formula given below.

The drug has been shown to be effective in combating most Gram-negative micro-organisms, including *Esch. coli*, *Klebsiella*, and *B. proteus*, *in vitro* and *in vivo* (Barlow, 1963; Buchbinder, Webb, and McCabe, 1962; Leshner *et al.*, 1962), though *Pseudomonas* appears to be more resistant (Barlow, 1963; Buchbinder *et al.*, 1962; Harper and Howse, 1964). Gram-positive bacteria such as staphylococci, enterococci, and streptococci have been described as resistant to nalidixic acid, when tested by the disc sensitivity method; however, satisfactory clinical responses to the drug have been shown by patients with these types of infections (Campbell, Thomley, and Parsons, 1964; Carroll, 1963; Zinsser, Dubow, and Seneca, 1964).

No severe reactions have been observed after the administration of nalidixic acid. Gastro-intestinal disturbances and vertigo (Auvray, 1964; Carroll, 1963; Harper and Howse, 1964; Reimann-Hunziker and Reimann-Hunziker, 1964; Slade, 1963), revers-

ible visual disturbances (Auvray, 1964; Carroll, 1963), drowsiness (Harper and Howse, 1964), mild depression (Slade, 1963), transient CNS disturbances (Cahal, 1965), and photosensitive skin rashes (Cahal, 1965; Schnitler, 1965; Zinsser, 1964) have been noted. The use of the drug in children has not been extensively described, but side-effects appear to be minimal (Carroll, 1964; Lackner and Potacs, 1964; Palmer, 1962; Reimann-Hunziker and Reimann-Hunziker, 1964; Schnitler, 1965; Williams 1965).

There are, so far, only a few published reports of the treatment of urinary tract infections in children. Schnitler (1965) treated 48 children with nalidixic acid for two weeks, and had good results in 37, moderately good results in 6, and poor results in 5 cases.

Methods and Subjects

In the present study, 35 children with urinary tract infection were treated with nalidixic acid in the period from summer 1964 to summer 1965. The regional distribution of the patients corresponded to the entire catchment area of the hospital, consisting of the whole of Lapland with 220,000 people, 3·6 inhabitants per square mile. Both urban and rural districts were represented. Some patients travelled 300 miles to reach the hospital. During the course of therapy, all were in-patients at the Children's Hospital, Lapland. Follow-up studies were performed on an out-patient basis.

The dose of nalidixic acid administered was adjusted in each case to correspond to a total of 60 mg./kg. day, in 3 or 4 doses. Infants were given the drug in the form of syrup, while the older children received tablets. The mean duration of therapy was 16 days; the shortest period of treatment was 14 days and the longest was 28 days.

Before and immediately after the treatment, a urine specimen was obtained, in all cases by catheterization, and microscopically examined. Ten or more leucocytes per high power field were taken as the criterion of infection. 5 ml. of the specimen was centrifuged, and the sediment was stained to show the presence of bacteria. These were cultured on blood-lactose and liver-bouillon agars, the incubation time being 24 to 48 hours. Differentia-

tion was by general biochemical reactions. In all cases but one, the bacterial culture was strongly positive, and the sensitivity of the strain to nalidixic acid was established before treatment. After 7 days, a clean voided sample of midstream urine was examined in the same way. The criterion of infection in this case was at least 20 leucocytes per high power field.

Various laboratory examinations were carried out before and immediately after the course of therapy. These included estimations of haemoglobin; packed cell volume; mean corpuscular haemoglobin concentration; white cell count; differential white count; thrombocyte and reticulocyte counts; SGOT; prothrombin time; and urea-nitrogen (this was controlled if found to be raised). The amount of residual urine immediately after micturition was estimated after catheterization, and controlled where necessary.

In 12 children, cystography and/or cystoscopy was carried out before or after intravenous pyelography. Interpretation of the results is beyond the scope of this study.

On the penultimate day of therapy, hydrocortisone 1.5 mg./kg. was given orally to each patient. The purpose of this 'cortisone provocative test' (Katz, Velasquez, and Bourdo, 1962) was to demonstrate, by the resulting pyuria, the presence of any residual infection.

Comparative studies of nalidixic acid and other drugs used in the treatment of urinary tract infections were also made, based on the sensitivity of bacteria found in the urine, both of patients included in the present series, and also of all the other patients in the hospital at that time.

Follow-up studies were carried out 1 month and 3 months after nalidixic acid therapy. If pyuria or bacteriuria was suspected on examination of a clean-voided specimen of urine, this was confirmed by examination of a specimen obtained by catheter.

The study included 34 girls and 1 boy, and they were classified under two headings. Group I comprised 23 children with pure primary infections, and Group II comprised 12 cases with previous histories of suspected or confirmed infections; 6 patients in this group had histories of severe infection, and, in these, treatment with nalidixic acid was followed by administration of other chemotherapeutic agents or antibiotics.

The age distribution of the children in the two groups is shown in Table I. The youngest child was 3½ months old, and the oldest was aged 11 years 8 months.

TABLE I
Age Distribution Between Groups

Age (yr.)	Group I	Group II	Total
< 1	6	1	7
1-5	8	3	11
5-10	8	8	16
> 10	1	—	1
Total	23	12	35

Results

Clinical findings. Table II shows the types of bacteria cultured from urine of untreated patients, and Table III shows the number of patients in both groups with bacteriologically sterile urine during and after therapy. Table IVA gives the number of relapsed and reinfected cases found 1 and 3 months after treatment. The infecting organism found in the Group I patient at the 3-month follow-up examination was thought to be the same strain of *Esch. coli* as that found before nalidixic acid therapy was instituted; this was therefore considered to be a relapsed case. One of the patients in Group I failed to attend for the second follow-up examination. The results of sensitivity tests suggested that, of the infections revealed by follow-up examinations in Group II patients, one was a re-emergent strain while the others were fresh infections. Of the children found to be harbouring an infection during the follow-up period, only one had been treated with other drugs after nalidixic acid.

Table IVB lists the various bacterial strains found, before and after treatment, in the urine of re-infected patients.

Radiological examination revealed one case of bladder papilloma which was treated by diathermy after nalidixic acid therapy. This Group II patient was later found to have a fresh infection of *Streptococcus faecalis*. In 2 children, micturating cystograms showed the presence of contracture of the bladder neck: in one of them, a bladder neck resection (Y-V plasty) was performed, with no

TABLE II
Micro-organisms Cultured from Urine Before Treatment

Group	Strain	No. of Strains Isolated
I	<i>Esch. coli</i>	18
	<i>Proteus mirabilis</i>	2
	<i>B. paracoli</i>	2
	Unknown	1
II	<i>Esch. coli</i>	10
	<i>Proteus mirabilis</i>	1
	<i>B. paracoli</i>	1

TABLE III
Number of Cases with Bacteria-free Urine During and After Treatment

Material	Cleared Urine After 1 Week's Treatment	Cleared Urine Immediately After Treatment
Group I	14	23
Group II	10	12

TABLE IVA

Number of Cases with Re-emergent or Fresh Infections after Treatment

Material	Relapses and Re-infections		
	1 Month After Treatment	3 Months After Treatment	Total
Group I	—	1	1
Group II	2	3	5

subsequent infection; in the other, cystoscopy revealed nothing abnormal, and an operation was not indicated. This patient was found to have a re-infection during the follow-up period. Urethritis was suspected in a patient with increased residual urine. Urethral dilatation was performed after nalidixic acid therapy. This Group II patient was also later found to have a re-infection.

Results of comparative sensitivity tests.

Sensitivity tests were carried out for different drugs by a modification of Ericsson, Högman, and Wickman's (1954) method using a special blood-glucose agar made by the Orion Company. The degree of circular inhibition of bacterial growth on the agar around the sensitivity test discs was taken as a measure of the efficacy of the various drugs. Inhibition was visually estimated by the same person at all times, and was allotted one of the symbols on the scale —, ±, +, ++, +++. Tables V, VI, and VII illustrate the comparative activities of various drugs against the micro-organisms cultured from urines of patients subsequently given nalidixic acid.

Resistant bacterial strains, cultured from the urines of the entire patient population of the hospital (including those selected for nalidixic acid treatment)

TABLE V

Activity of Various Drugs Against *Esch. coli* (28 strains)

Drug with Concentration per Disc	+++	++	+	±	—
Nalidixic acid (30 µg.) ..	1	17	10	—	—
Sulphadiazine (2.4 mg.) ..	15	4	1	3	5
Kanamycin (5 µg.) ..	—	—	15	12	1
Streptomycin (50 µg.) ..	1	13	11	2	1
Terramycin (50 µg.) ..	—	4	13	3	8
Tetracycline (50 µg.) ..	—	1	13	5	9
Chloramphenicol (30 µg.) ..	1	9	10	4	4
Nitrofurantoin (0.03 mg.) ..	—	13	11	4	—
Doctacillin (20 I.U.)* ..	1	10	6	2	1
Colimycin (10 µg.) ..	3	20	5	—	—

* Sensitivity estimation with doctacillin was not performed in 8 cases.

TABLE IVB

Micro-organisms Cultured from Urines of Patients with Fresh Infections after Treatment

Micro-organisms Cultured From Same Patient	
Before Treatment	After Treatment
<i>Esch. coli</i>	<i>Streptococcus faecalis</i>
<i>Esch. coli</i>	<i>Esch. coli</i> (another strain)
<i>B. paracoli</i>	<i>Esch. coli</i>
<i>Proteus mirabilis</i>	<i>Proteus mirabilis</i> (another strain)

are listed in Table VIII. The criterion of 'resistance' to the various drugs was taken to be a rating of — or ± for the sensitivity estimation.

Side-effects. No pathological changes in the blood picture, reticulocyte, and thrombocyte counts, prothrombin times, or SGOT values were observed. 6 patients showed minor side-effects: 4 children less than 1 year old suffered mild gastro-intestinal disturbances which disappeared during the treatment; a 4-year-old girl complained of skin irritation during treatment, and a girl of 3 developed a maculo-

TABLE VI

Activity of Various Drugs Against *B. Paracoli* (3 strains)

Drug with Concentration per Disc	+++	++	+	±	—
Nalidixic acid (30 µg.) ..	—	2	1	—	—
Sulphadiazine (2.4 mg.) ..	3	—	—	—	—
Kanamycin (5 µg.) ..	—	—	3	—	—
Streptomycin (50 µg.) ..	—	2	1	—	—
Terramycin (50 µg.) ..	—	—	2	—	1
Tetracycline (50 µg.) ..	—	—	3	—	—
Chloramphenicol (30 µg.) ..	—	1	2	—	—
Nitrofurantoin (0.03 mg.) ..	—	—	3	—	—
Doctacillin (20 I.U.)* ..	—	—	1	—	—
Colimycin (10 µg.) ..	—	2	1	—	—

* Sensitivity estimation with doctacillin was not performed in 2 cases.

TABLE VII

Activity of Various Drugs Against *Proteus Mirabilis* (3 strains)

Drug with Concentration per Disc	+++	++	+	±	—
Nalidixic acid (30 µg.) ..	—	2	1	—	—
Sulphadiazine (2.4 mg.) ..	—	—	—	1	2
Kanamycin (5 µg.) ..	—	—	3	—	—
Streptomycin (50 µg.) ..	—	—	1	—	2
Terramycin (50 µg.) ..	—	—	—	—	2
Tetracycline (50 µg.) ..	—	—	1	—	—
Chloramphenicol (30 µg.) ..	—	1	—	2	—
Nitrofurantoin (0.03 mg.) ..	—	—	1	2	—
Doctacillin (20 I.U.) ..	—	—	—	2	1
Colimycin (10 µg.) ..	—	—	1	—	2

TABLE VIII

Number of Bacterial Strains Showing Resistance and Percentage Resistance to Various Drugs*

Drug	<i>Esch. coli</i>	<i>B. paracoli</i>	<i>Proteus</i>				<i>Klebs. aerob.</i>	<i>Pseudo-monas</i>	<i>Alcalig. faecalis</i>	Total Resistant
			<i>mirab.</i>	<i>rettg.</i>	<i>vulg.</i>	<i>morg.</i>				
Nalidixic acid ..	11 (6)	4 (16)	6 (15)	0 (0)	0 (0)	0 (0)	14 (47)	13 (100)	1 (33)	49 (17)
Sulphadiazine ..	33 (19)	6 (24)	29 (74)	4 (80)	3 (50)	2 (100)	11 (37)	4 (31)	0 (0)	92 (31)
Kanamycin ..	68 (40)	2 (8)	30 (77)	2 (40)	2 (33)	2 (100)	6 (20)	12 (92)	2 (67)	126 (43)
Streptomycin ..	24 (14)	2 (8)	27 (69)	1 (20)	1 (17)	1 (50)	14 (47)	4 (31)	3 (100)	77 (26)
Tetracycline ..	56 (33)	12 (48)	38 (97)	3 (60)	5 (83)	1 (50)	24 (80)	13 (100)	3 (100)	155 (53)
Chloramphenicol ..	63 (37)	10 (40)	38 (97)	3 (60)	5 (83)	1 (50)	24 (80)	13 (100)	3 (100)	160 (55)
Nitrofurantoin ..	41 (24)	7 (28)	12 (31)	1 (20)	1 (17)	0 (0)	24 (80)	12 (92)	2 (67)	100 (35)
Doctacillin*†	8 (5)	2 (8)	21 (54)	5 (100)	2 (33)	1 (50)	20 (67)	13 (100)	2 (67)	74 (25)
Colimycin (10 µg.) ..	31, 37 (18, 23)	7, 6 (28, 37)	27, 10 (69, 93)	3, 2 (60, 100)	3, 2 (50, 75)	1 (50, 100)	22, 6 (73, 92)	9, 4 (69, 100)	1, 2 (33, 100)	104 (36)
Total number of strains examined ..	170	25	39	5	6	2	30	13	3	293

* Figures in parentheses are percentages.

† Figures in italics indicate cases in which sensitivity estimations were not carried out, because of shortage of test discs. Figures in bold (bracketed) indicate percentage resistance of total strain actually examined.

popular rash on her body and limbs after 12 days' treatment. The rash disappeared some days after the end of therapy.

Discussion and Conclusions

The purpose of this clinical trial of nalidixic acid was to assess the value of this new drug in combating acute urinary tract infections. We were also interested in its possible role in the management of acute episodes in chronic infections, and wished to know what side-effects, if any, might occur in infants and children receiving the drug.

In all but one of the children in the present series, the sensitivity of the infecting micro-organism to nalidixic acid was established before administration of the drug. Had the material not been selected in this way, it is possible that different results might have been obtained (Schlegel, 1962).

Preliminary results obtained immediately after treatment were good in all cases. The samples obtained after one week's therapy showed the urine to be sterile, and this was borne out by the clinical findings. This is a strong indication that the drug is suitable for treating primary urinary tract infections and acute episodes in chronic cases, in paediatric practice.

Treatment was continued for about two weeks: this has been shown in adult practice to be a safe and effective period of therapy (Cahal, 1965), and the follow-up period was fairly protracted. This seems to provide a treatment of adequate duration for the eradication of pure primary infections, if sensitivity of the infecting micro-organism has been established previously. Of the 5 infections found in Group II patients during the follow-up period, 4 were fresh infections; only one of these patients had received

other drugs after nalidixic acid. Pyuria was not produced by the cortisone provocative test in those patients in whom a fresh infection was subsequently found.

The results of *in vitro* sensitivity tests with nalidixic acid are in agreement with those reported elsewhere (Barlow, 1963; Buchbinder *et al.*, 1962; Lesher *et al.*, 1962). The activity against various strains of proteus appeared to be high, but unfortunately only a few proteus-infected cases could be included in the trial. Nalidixic acid activity appeared to be quite good against all Gram-negative bacteria except pseudomonas. It is possible that this picture may change if the drug comes into widespread use, because of the development of resistant strains (Barlow, 1963; Gandelman and Mann, 1964).

The few side-effects noted were insignificant and reversible. However, several out-patients who received nalidixic acid but who were not included in the present trial also suffered gastro-intestinal disturbances. Although these disorders have been shown to regress as treatment continues, occasionally therapy should be discontinued in out-patients.

Summary

35 children with urinary tract infections were treated with nalidixic acid. 23 of them had primary infections, and 12 had previously had one or more suspected or confirmed infections. The dose administered corresponded to 60 mg./kg. day, in 3 or 4 instalments. The mean duration of therapy was 16 days. Preliminary results obtained immediately after treatment were good in all cases. Side-effects were minimal, and no haematological, neurological, or hepatic complications were observed. One re-emergent infection was found in both

groups during the follow-up period. Four fresh infections were found in the group which had had previous suspected or confirmed infection.

The Winthrop Products Company kindly provided materials for this study.

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